

Presidential Commission for the Study of Bioethical Issues

- Meeting 11
- November 5, 2012
- Chicago, Illinois

Anthrax Vaccine Trials in Children: Research and Risk in Mass Casualty Medicine

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November 5, 2012



Plague on the Stairs
Theodore Kittelsen

Illustration of the
Black Death (from a
child's perspective)

1896: Norwegian
artist

National Commission: Research Involving Children

- Exceptional Circumstances
- Failure to involve children in research may exceed whatever risk is presented by that research...
- For instance, the threat of an epidemic that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable..."

Paul Ramsey

- “To experiment on children in ways that are not related to them as patients is already a sanitized form of barbarism.”
- Richard Miller critique of Ramsey is that he conflates beneficence with autonomy (requiring that research show a benefit before parents allowed to consent/permission.)
- Paul Ramsey, *The Patient as Person*, New Haven, Yale University Press, 1970: pg. 35.
- Richard B Miller, *Children, Ethics and Modern Medicine*, Indiana University Press, 2003: pg. 244.; see Chapter 11: Ethical Issues in Pediatric Research.

Ramsey

- “No parent is morally competent to consent that his child shall be submitted to hazardous or other experiments having no diagnostic or therapeutic significance for this child himself.”
 - Ramsey: 18

Ramsey

- “Recognizing that banning children from nontherapeutic research would leave them without adequate medications and available therapies, he exhorted researchers to ‘sin bravely’: the ethically trustworthy investigator would be one who did not ‘deny the moral force of the imperative he relates.’”
- Paul Ramsey, “The Enforcement of Morals: Non-Therapeutic Research on children,” *Hastings Center Report* 6 (1976):24. in Miller: pg. 244

- Therapeutic orphans
- Are we being over protectionist
- Do we harm children as a class
- Off label use of new molecular entities
(FDA list of ten drugs widely used for children with no or inadequate labeling for use with children: albuterol, zoloft, ritalin, prozac [3000 xs for children younger than one) [Miller]
- How do we assess risks
 - Miller, Richard B. Children, Ethics and Modern Medicine 2003; Indiana University Press: pg. 241

The Other Orphans: A Not So Apt Analogy

- “Reasoning well about risk is most challenging when a woman is pregnant, for patient and doctor alike. During pregnancy, we tend to note the risks of medical intervention without adequately noting those of *failing* to intervene, yet when it’s time to give birth, interventions are seldom questioned, even when they don’t work. Meanwhile, outside the clinic, advice given to pregnant women on how to stay healthy in everyday life can seem capricious and overly cautious.

Risk and the Pregnant Body

- This kind of reasoning reflects fear, not evidence.
 - Lyerly et al, “Risk and the Pregnant Body,” *Hastings Center Report* 39, no. 6 (2009):34-42.

Biological-Chemical Agent Threat Classification

- The Ethics of Coercion in Mass Casualty Medicine
- Griffin Trotter, MD, PhD
- The Johns Hopkins University Press
- 2007

Three Categories of Threat Classification

- Appropriate levels of agency
 - In context of clinical medicine, justification for coercion
-
- Trotter: pg. 80

Three Categories of Threat Classification

- 1. Duration prior to effects
 - “the length of the critical latency period that may exist between an attack or the initiation of an event and the development of clinical symptoms or other signs of damage”
 - D₁ = duration of 0-1 hour (immediate)
 - D₂ = duration of 1-24 hours (intermediate)
 - D₃ = duration of greater than 24 hours (prolonged)
- Trotter: pg. 61

Three Categories of Threat Classification

- 2. “Lethality: Likely to be lethal (L₁) or not likely to be lethal (L₂)
 - L₁ = mortality rate at ten percent or higher
 - “Even a relatively low mortality figure like ten percent can cause mass dying when large numbers are affected.”
-
- Trotter: pg. 82

Three Categories of Threat Classification

- 3. “Transmission: likely and not likely
 - Likely = agent known to have caused epidemics or to have the potential to cause epidemics
 - Trotter: pg. 82

Categories

- Six “Category A” biological weapons agents (D₃, L₁, T₁)
- Three are highly transmissible human to human
 - Smallpox (*Variola major*)
 - Plague (*Yersinia pestis*)
 - Hemorrhagic Fevers

- Trotter: pg. 81

Category and Agency

- D₃L₁T₁
- Require Federal Agency in planning and implementation

Categories

- Others: local or state jurisdiction with federal assistance as requested
 - Anthrax (*Bacillus anthracis*)
 - Botulinum toxin
 - Tularemia (*Francisella tularensis*)
- Trotter: pg. 81, 82

Trotter's Admonition

- “Smallpox, plague and the hemorrhagic fevers require a special approach and should be regarded as a distinct threat category.”
- “To lump these agents together in a single category, as we now do, invites confusion among rescuers, clinicians, and the public – a fact confronted regularly by those of us who have tried to import information about biological terrorism.”
- Trotter: pg. 81

Categories and Agency

- Federal assistance may be required with anthrax:
 - Stockpiling antibiotics for large scale attack
 - Laboratory and forensic technology

Risk and Preparedness

- US National Biodefense Science Board supports clinical trials
- Broad guidance by National Commission
- Public discourse and deliberation: Presidential Commission for the Study of Bioethical Issues
- Disagreement among experts in disaster preparedness, pediatrics, research ethics
- And then,

Risk and Preparedness

- 407 Panel
- Paradox of assessing risk of harm to healthy children in the context of uncertainty about the risk

Antinomians Rule

- ? First 407 Panel
- 2001
- Basement in Bethesda/weekend
- Ernie Prentice, Skip Nelson, Dale Hammerschmidt, and self
- Three protocols
- No review but a letter suggesting process and definitions
- Research Ethics Dweebs: Federal research regulations on cell phones
- Define “serious!”

Risk and Preparedness

- What interest does a healthy child have in remaining healthy
- Ethics of Care: Recognizing a Need, Establishing a relationship, Being competent and responsible within one's role
- What does it mean to be a “good” parent?
- What does it mean to be a “good” clinical investigator?
- Etc.

CTSI

- Research institutions with NIH-awarded Clinical Translational Science Institutes
- Mandatory Research Ethics Consultation
- Another expert body could be a working group of CTSI research ethics consultants

Risk and Preparedness

- 407 Panel will have benefit of proposed protocols
- 407 Panel will thus have benefit of proposed informed consent documents
- 407 Panel will have benefit of your deliberations
- Scientific rationale for pre-event study?
- Healthy children: those who may be most vulnerable cannot assent or dissent/refuse participation in research (sufficiently able to extrapolate data?)
- Lethality of agent (anthrax = 75% mortality) argues for prevention trial(s)

Ultimately

- How do we define or know the vaccine is “safe and effective” without doing the research? The individual child and the collective individual.
- Not to decide is to make a decision
 - Joseph Francis Fletcher

It is difficult
to get the news from poems
yet men die miserably every day
for lack
of what is found there.



Excerpt from "Asphodel, That Greeny Flower"

